

Improving detection and management of drug allergy

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Improving detection and management of drug allergy

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FIGURE 1

A patient with lip angioedema four hours after taking aspirin

What are the mechanisms involved?



THE TERM DRUG ALLERGY IS NON-SPECIFIC AND WIDELY MISUSED. OFTEN THE DIAGNOSIS IS ASSUMED

with little definitive evidence.

As well as the risk of overdiagnosis, underreporting is also a problem. Investigation is frustrated by limited availability of reliable confirmatory tests. The clinical guideline published by NICE, in September 2014, gives evidence-based recommendations on diagnosis, management, and advice on when to refer to specialist clinics.¹

Suspected adverse drug reactions may be subdivided in a variety of ways. Classification may be on the basis of mechanism e.g. immunological (requiring sensitisation by previous exposure) versus non-immunological; timing (e.g. immediate or delayed), or

What investigations should be carried out?

whether the phenomenon is dose dependent or not.

'Rash and/or mucosal reactions are common adverse drug effects'

In the recent NICE guideline¹ the main approach adopted is to classify the adverse event according to whether it is immediate (within an hour of drug administration) or delayed (hours or days), and whether it affects a single system (e.g. only cutaneous such as urticaria) or multiple systems, and whether

Which patients should be referred?

clinically severe/life threatening or not.

Rash and/or mucosal reactions are common adverse drug effects. Urticaria (caused by NSAIDs, for example), angioedema (e.g. aspirin, see figure 1, above; ACE inhibitors), maculopapular rash (e.g. antibiotics), photosensitivity (e.g. tetracycline), erythema multiforme (e.g. NSAIDs), and Stevens-Johnson syndrome (e.g. allopurinol) provide examples which reflect the wide range of different mechanisms (many non-immunological) and the range of clinical severity.

The point is made that gastrointestinal manifestations in isolation have a low specificity for true drug allergy, although GI disturbance after antibiotics is well recognised.

An immediate, immunologically mediated, multisystem, life-threatening »

SPECIAL REPORT

DRUG ALLERGY

reaction would for example include anaphylaxis (type 1 or typically IgE-mediated hypersensitivity), especially if the clinical features (e.g. bronchospasm, hypotension) are suggestive.

INVESTIGATIONS

Cross-reference is made to the 2011 NICE guideline on investigation and management of anaphylaxis² with a reminder to test acutely (ideally within two hours and certainly before four hours post reaction) for serum mast cell tryptase, as previously reviewed in this journal.³ Total serum IgE testing is not useful and not recommended.

Detailed investigation of suspected cases in a specialist clinic is ideally delayed for 4–6 weeks after the event, and skin testing is the main test modality used.^{4,5} Blood testing is limited, and

‘Patch testing is not recommended for high-risk cases where previous reactions have been life threatening’

suffers from a very limited repertoire and low sensitivity.

For some, but not all, drugs implicated in an immediate possible anaphylactic reaction, skin prick testing which may be followed by more sensitive and more risky intradermal testing may be definitive (this is indicated for local and general

anaesthetic or penicillin reactions, but is not useful for NSAID testing).

For delayed reactions, where an immunological mechanism (T-cell mediated) is suspected, patch testing (skin patches loaded with drug embedded in paraffin wax) may be useful (e.g. maculopapular rash following antibiotic use) but again sensitivity is low.

Patch testing is not recommended for high-risk cases where previous reactions have been life threatening including Stevens-Johnson syndrome.

Patients referred to a specialist clinic for skin testing should, if possible, suspend any medication that may potentially interfere with testing (antihistamines, prednisolone, and others). The two case reports below provide illustrative examples.

Case 1

Immediate type/anaphylactoid reaction

A 45-year-old man developed generalised urticaria, lip angioedema, cough and wheeze within 30 minutes of taking two tablets of naproxen 250 mg and amoxicillin 500 mg immediately before tooth extraction.

His previous history included mild asthma (for which he used a salbutamol inhaler as required), and chronic back pain. Questioning revealed previous urticaria and/or angioedema episodes associated with ibuprofen and diclofenac. He had tolerated amoxicillin on several occasions before, but this was his first use of naproxen.

Paramedics arrived within 20 minutes. Low systolic pressure (60 mmHg) was documented. Adrenaline 0.3 mg was given IM, and other measures included normal saline infusion, nasal oxygen, nebulised salbutamol, chlorpheniramine (10 mg) and hydrocortisone 100 mg IV. He was kept in hospital for six hours under monitoring and discharged with a three-day course of oral cetirizine 10 mg and prednisolone 30 mg daily.

He was advised to avoid all NSAIDs and beta-lactam antibiotics until he had been assessed in the specialist allergy clinic. Mast cell tryptase samples taken 90 minutes and four hours post-event later showed markedly elevated levels indicating a mast cell-mediated process (not necessarily anaphylaxis) but subsequent clinic samples confirmed that tryptase levels had returned to normal.

Six weeks later, normal/negative skin prick testing was followed by intradermal testing against penicillin derivatives, and benzylpenicillin, ampicillin and amoxicillin. With written consent, a drug provocation test with oral amoxicillin was carried out which was successful ruling out the latter as the culprit. It seemed likely that he had suffered an anaphylactoid reaction to naproxen and should therefore avoid all NSAIDs. (Skin tests are almost always unhelpful for aspirin and NSAIDs, and were not performed).

At follow-up, a supervised graded challenge with meloxicam was uneventful. He was given a MedicAlert application (NSAID intolerance but meloxicam safe to use) and a copy of the discharge letter. He was advised to discuss optimal control of his asthma with his GP.

Case 2

Delayed type hypersensitivity reaction

A 27-year-old woman presented to her GP with a pruritic rash on her trunk on the third day of using amoxicillin/clavulanic acid for sinus infection. Physical examination revealed a maculopapular rash but no desquamation, blisters or pustules. Acute general blood tests (full blood count, liver and renal function) and mast cell tryptase levels were all normal. The antibiotic was discontinued and a prescription of oral steroids and antihistamines was given. Her symptoms resolved within a week.

The patient recalled that she had had a similar, but milder, skin rash at the end of an amoxicillin course three years before. No other history of suspected drug allergy was reported. A mild, delayed, immunological, T-cell mediated reaction seemed most likely.

There was debate as to whether testing was necessary, as there was no reason not to avoid penicillins in favour of alternative antibiotics as and when required. However, the patient was keen to undergo testing and was referred to a specialist in a private clinic where both skin prick and intradermal testing with penicillins were negative, as expected.

Patch testing was judged not to be worthwhile. However, the patient was advised to monitor test injection sites over the next few days and to photograph any skin changes. An erythematous infiltration around both the amoxicillin and the amoxicillin/clavulanic acid intradermal testing site was noticed at 72 hours. Clinical history and skin test pointed to a type IV (delayed, T-cell mediated) reaction to amoxicillin. She was advised to avoid all beta-lactam antibiotics. Cross-reactivity between penicillins and cephalosporins is predicted to be very low for T-cell mediated responses.

A MedicAlert application (delayed allergy to penicillin) and a copy of the clinic discharge letter were given to the patient and her GP.

key points

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Suspected adverse drug reactions may be subdivided

on the basis of mechanism e.g. immunological (requiring sensitisation by previous exposure) versus non-immunological; timing (e.g. immediate or delayed), or whether the phenomenon is dose dependent or not. In the recent NICE guideline the main approach is to classify the adverse event according to whether it is immediate (within an hour of drug administration) or delayed (hours or days); affects a single system or multiple systems; is clinically severe/life threatening or not.

An immediate, immunologically mediated, multisystem,

life-threatening reaction would for example include anaphylaxis (type 1 or typically IgE-mediated hypersensitivity) especially if the clinical features (e.g. bronchospasm, hypotension) are suggestive. Serum mast cell tryptase should be tested ideally within two hours and certainly before four hours post reaction. Detailed investigation of suspected cases in a specialist clinic is ideally delayed for 4-6 weeks after the event, and skin testing is the main test modality used.

Adverse drug reactions need to be meticulously recorded

and the patient and their family should be fully informed. Documentation should include: date of reaction; drug name (chemical and generic); route of administration; time interval between first dose and event; and nature and severity of symptoms. Written guidance should be provided on which other chemically related drugs also need to be avoided.

Patients with mild reactions (e.g. isolated urticaria)

following a non-selective NSAID who have an ongoing need for anti-inflammatory medication could be considered for a trial of a selective COX-2 inhibitor, which carries a lower risk of further urticaria, started at a low dose, without specialist referral. However, this approach would not be recommended when the previous adverse NSAID reaction was more severe (e.g. an asthma episode requiring nebuliser treatment).

Specialist referral is indicated for the following: all cases

of suspected anaphylaxis; all severe/life-threatening episodes e.g. Stevens-Johnson syndrome; severe NSAID reactions with ongoing need for NSAID therapy; suspected penicillin allergy (but only where alternative antibiotics are not available); and problems related to general and local anaesthesia.

RECORDING DRUG REACTIONS

A key recommendation in the NICE guideline¹ is that adverse drug reactions need to be meticulously recorded, and that the patient and their family should be fully informed. This information also needs to be made available to other healthcare professionals in primary and secondary care.

One recommendation from NICE is that all GP referrals and all hospital discharge summaries include this information as a matter of routine including documentation of 'no known drug allergy' as appropriate.

'Adverse drug reactions need to be meticulously recorded and the patient and family fully informed'

Documentation should include:

- Date of reaction
- Drug name (chemical and generic)
- Route of administration
- Time interval between first dose and event
- Nature and severity of symptoms

Written guidance should be provided on which other chemically related drugs also need to be avoided. It is important, for example, that a patient who has experienced urticaria following diclofenac is also aware that the drug's brand name is Voltarol, and that it is a member of the NSAID family all of which may trigger similar (non-immunological) reactions.

REFERRAL

Patients with mild reactions (e.g. isolated urticaria) following a non-selective NSAID who have an ongoing need for anti-inflammatory medication could be considered for a trial of a selective COX-2 inhibitor, which carries a lower risk of further urticaria, starting at a low dose without specialist referral.

However, this approach would not be recommended when the previous adverse NSAID reaction was more severe (e.g. an asthma episode requiring nebuliser treatment).

Specialist referral is indicated for the following:

- All cases of suspected anaphylaxis
- All severe/life-threatening episodes

e.g. Stevens-Johnson syndrome

- Severe NSAID reactions with ongoing need for NSAID therapy
- Suspected penicillin allergy (but only where alternative antibiotics are not available)
- Problems related to general and local anaesthesia

Every referral is extremely time consuming in terms of skin testing which requires a day case slot. Each case of suspected penicillin allergy takes a specialist nurse an hour or so, and test-negative cases must still undergo penicillin challenge after written informed consent to confirm non-sensitivity which takes a further couple of hours.^{5,6} Hence where possible it is simpler just to flag such cases as possible allergy/intolerance and provide alternative antibiotics instead.

CONCLUSION

Drug allergy is a complex and potentially lethal problem. The recent NICE guidance¹ focusses on the need for full and proper documentation and communication, not least to the patient and their family. Detailed management advice is available from specialist clinics.

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Useful information

Allergy UK
www.allergyuk.org

British Society for Allergy and Clinical Immunology (BSACI)
www.bsaci.org

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